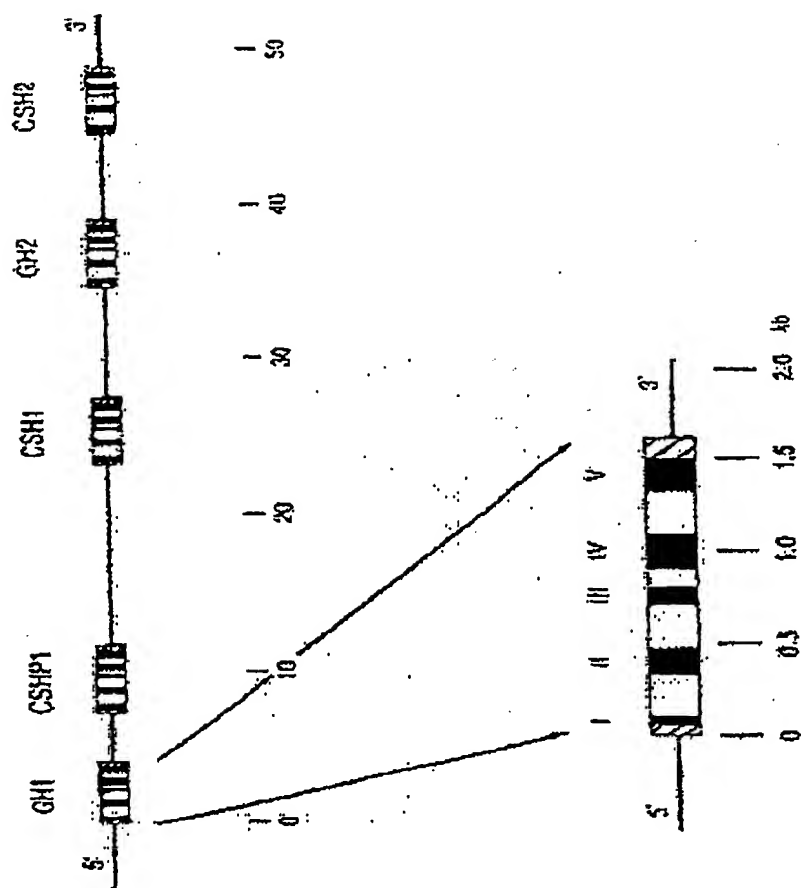


**Figure 1**



**Fig. 1** Human growth hormone gene cluster on chromosome 17q23. The fine structure of the GH1 gene is shown below. The scales are in kilobases (kb).

Figure 2

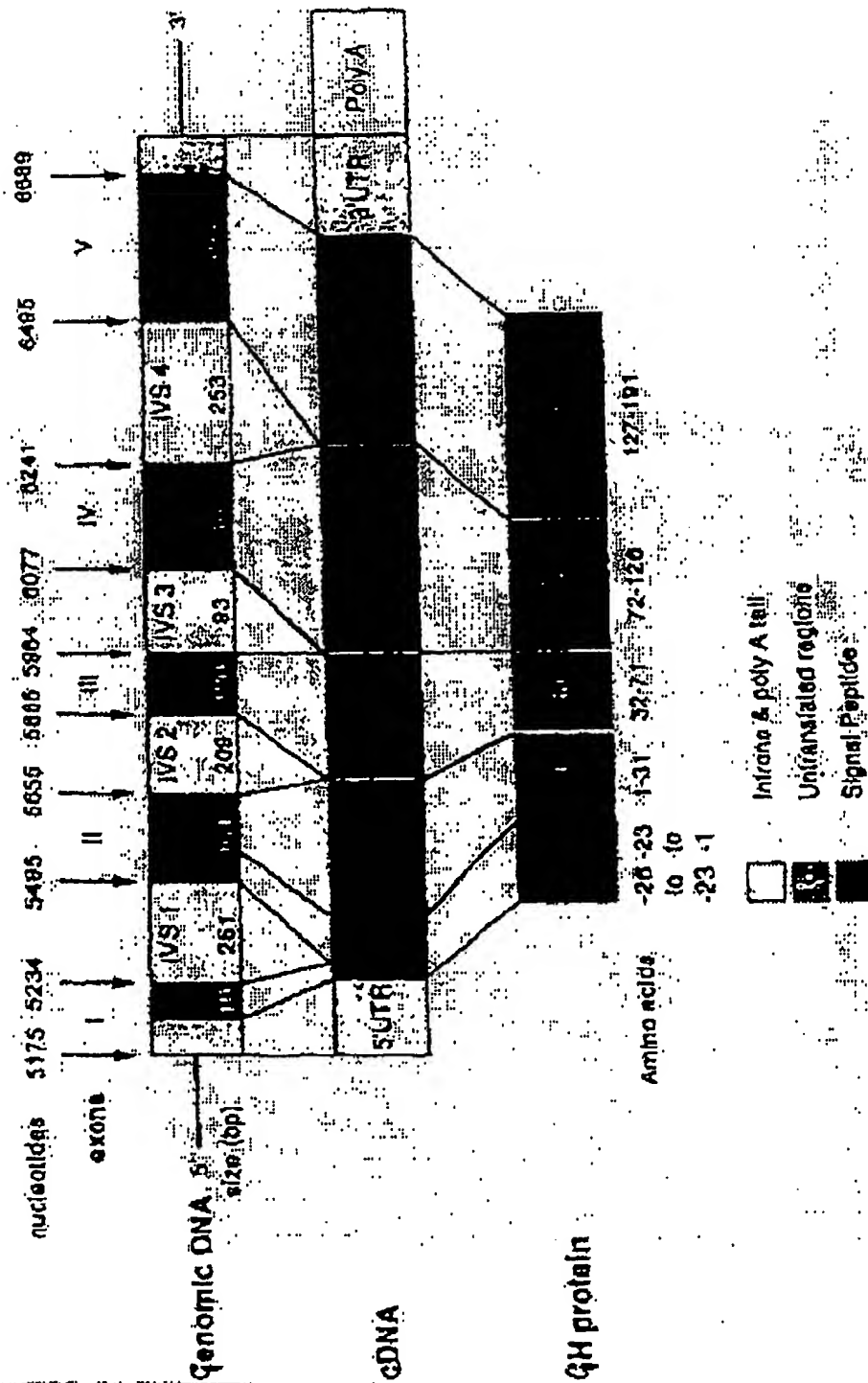


Figure 3

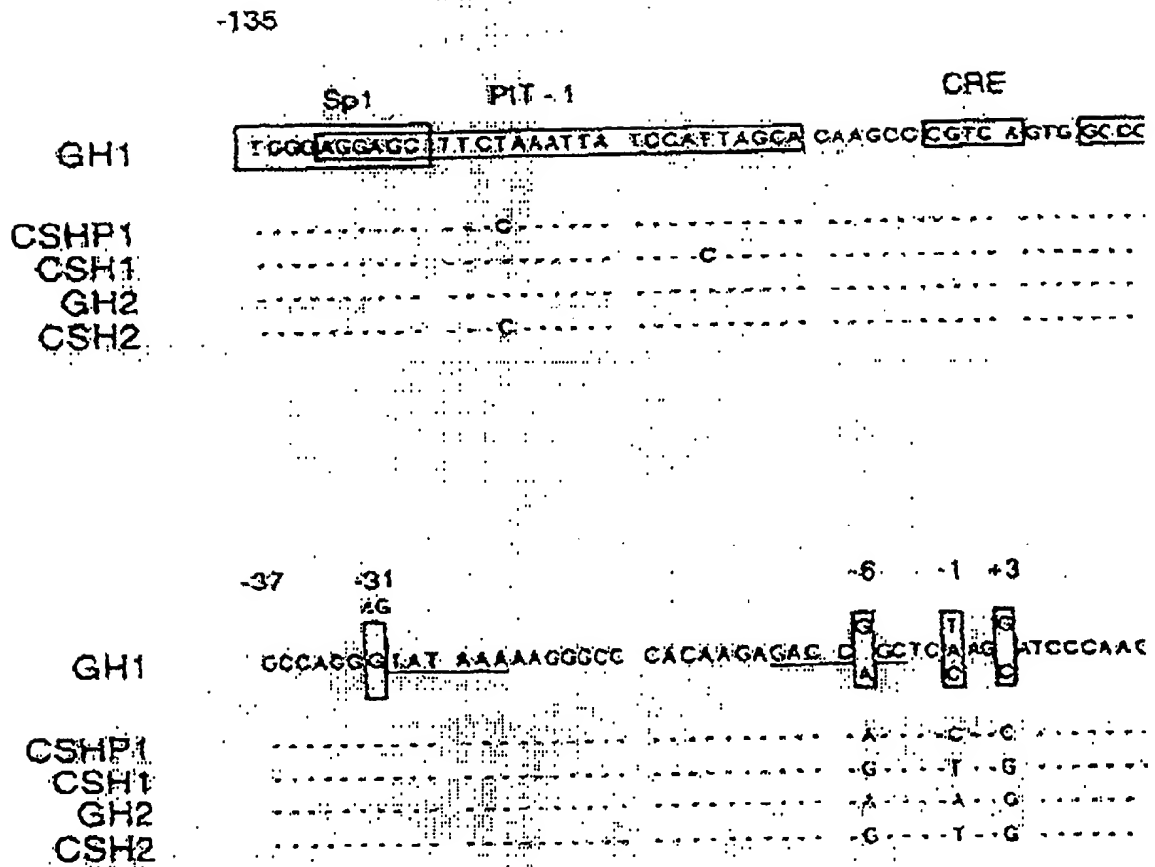


Fig. 3. Structure of the 5' untranslated region and promoter region of the human *GH1* gene. Horizontal boxes denote known, putative or inferred binding sites for transcription factors. Vertical boxes indicate polymorphic sites in the human population (data from Giordano et al. 1997; Wagner et al. 1997). The numbering scheme is by reference to the transcriptional initiation site at +1. The TATA box, a Chi-like element and the ATG translational initiation site are underlined. The human *GH1* promoter is also aligned with the promoters of the human *CSHP1*, *CSH1*, *GH2* and *CSH2* genes in order to indicate both the extent of homology but also the differences evident between promoters.

**Figure 4**

cccatgccatgggttggaaggcagaggggtctgggtggtccctctttagatcttggcctaggcctcgacctgataa 1-75  
5 gggtaacggtaccaacctccgtctccagagaccaccagggagaaaatctagaaccggatccggagcctggactatt  
ggtagggggccactctcaaggggtgcaggccaggacctgagccacggaagtcaggggcaggaggggttaagggttca 76-150  
ccacccccggtgagagttccccacgtccggtcctggactcgtgccttcagtcctccgctccccaattccaaagt  
tccgagggaacagccccgttccgggcagccccagatgttcttctgtttccagatgttccaaaatgaaaaacattt 151-225  
aggctccttgtcgggcaaggcccgctcggggtctacaagaaagaaaggtctacaagggttactttttgtaaa  
ctctgaaaagctgtcagatgttcagttcatggaataaaacagctcagaaaatataaacatcacctgaggtcagcttg 226-300  
gagacttttcgacagttctacaagtcagtagcttattgtcgagttcttatattttagtgagctccagtcgaac  
15 agggcccatggggccgcagctggtgaggggtggtgagagagactgacccgggggagtgggggcaaaaatctggga  
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gtctcatgggttaggaaaatactcttccctgagccccctaacgacagagtccttcatcttgggggtagtgctc 376-450  
cagagtaccaaaatcctttatgagaaggactcggggattgctgtctcaggaagtaattgaaaccccgatcacagag  
451-525  
cccaaaagtgggggggtataaactgggaaaggcttggggcacacgtgttctgggggggtgtgtgtgtgtgtatgt  
gggttcaaccccccatattgacctttccgaacccccgtgtgcacaaacacccccccacacacacacacataca  
526-600  
25 gcatgctcacacaggtgtgttgctcgctggacctgtggtgtggggcctactctggagctggtcctagggtcagcgg  
cgtacgagtggtccacacacagcgacctgggacacacacacccccggatgagacctcgaccaggatcccgagtcgcc  
601-675  
actgtaggggggcagggaggttggtggggggcagttggcaccatcctcaggtgacaggtgcgctaaaaatctcaga  
tgacatccccctgcctccaacccccccgtcaaccgtgggtaggagtcactgtccacgcgatttttagagtct  
676-750  
aatcaccactaaaagaacttatccaggtaacccaaaaaactacctgtaccccgaaaaaatattgaaataaaaaattt  
30 ttagtggtgatttcttgaataggtccattgggttttttttgatggacatgggggtcttttataactttattttttaa

751-825  
aaaaaaaaaagtgagaaagcagctcccactccaggagggaagacacacacatcccgtggacaaggatgcagatgt  
tttttttgtcactcttcgtcgagggtaggtccctccctctgtgtgtgtagggcacctgttcctacgtctaca

5 ggcctttgggcttcattcccatcctgcccgggcaggatctgttttcaggaggggcgaggagcggggcccca 826-900  
ccggaacccgaagtaaggtaagtaacggccctccctagacaaaagtccctccgcctccgtcgcccccggggt

ccgcctgcagggttatttgtcacattttgagcgtgctgttcctcactggtgacaaacagccctgagccccattt 901-975  
ggcgagcgtcccaataaacagtgtaaaactcggcacgacaaggagtgaccactgttgtcgggactcggggtaaa

10 tgggctcatgatgcccccttttctccagaaacaggagggcctcacaaagcctacccctgcctctgcctcggtgccc 976-1050  
acccgagtactacgggaaaagaagggtcttgcctccggagtgttcggatgggacggagacgggacggg

ggggcttcacattctgacttctgacgacacctccctttccaggaaaggcaacatcaaaataaggaaatgggggccag 1051-1125  
ccccgaagtgaagactgaagactgctgtggagggaaggctcctccgttgtagtttattccttaccctccgggtc

15 ggtcgggcgaagggacaaagggtcagggggtggggaaagcaagaaaggcagccccccagccctaggatgcc 1126-1200  
ccagcccgctccctgttccccgagtcctcccccaccccttcgttctccgtcgctgggggtcgggtccctacgg

20 gggagggggaagaaacctcagggaagaaagagctcagacccctgcctccttctccagcccggtgtcctggatctg 1201-1275  
ccctcccccttcttgagtccttcttctcgagctggtgggacggaggaagaggtcggtccacaggacctagac

ctgggctgctgactgggaaaaagacctgctaagaaggacgtgggtttgagtcctgacccagcagtgtagcagcc 1276-1350  
gaccgcgacgacctgaccttcttgacgattcttctgcacccaaactcaggactgggtcgtcacatcgtcgg

25 aggaaacctccccaggttaccagtggttctactaagggtggtctgccccaaacggaggagcgtctgcacatg 1351-1425  
tcctttggagggtccaatggtcaccgaagatgattcccaccgagacgggggttgctccctcgtcagacgtgtac

catcaggggcaatcgcgctggtctcaatgaccgggtgggtgcctggggcgaggagggttcattggctggcaagcagag 1426-1500  
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30

ttccctgccccacatgccaaacagcaccatgaggcaacaccattcttaacctctcagtgaccaaggttcctcat 1501-1575  
aagggacgggtgtacggttgctgtgggtactccgttgtggtagaagtggagagtcactggtccaaggagta

tttcgtaaaatagaaaataagcccaatagcgcgttttttgttgtgtttttctggggtttttctgagacaagatct 1576-1650  
5 aaagcattttatcttattcgggttatcgcgcaaaaaaacaacaaagaccccccaaaagactctgttctaga

tgtctgtgtgtccagggtggagtgcagtgggtgcaatctccattcacgggcaacctctgccacctggactcaagtga 1651-1725  
acgagacaacagggtccgacctcacgtcacccacgttagaggtaagtgcgttgagacggtggacctgagttcact

10 ttacccacctcagctcccgagtagctggactacaggtcatgtactacacctggtaattctgtgtatttctt  
aagtgggtggagtcggagggtctcatcgacctgatgtccagtagcatgatgtggaccgattagacacataaagaa

gtagagacaggttttactatgttgcccaggctggtctcaaaactcctgagctcaagcgatccacccgctcagcct 1801-1875  
catctctgtccaaaatgatacaacgggtccgaccagagtttgaggactcgagttcgtaggtgggcggagtcgga

15 cccaaagtgtgggtattacaggcgtgagccactgcgccccggcccccaacagtgcgttggtcgaaagggcagctgtgc  
gggtttcacgaccctaattgtccgactcggtagcgcgggcggggtgtcacgcaaccagcttcccgtcgacacg

acattgaaggccatcctgcattcgtgaggtacttggatgtggtggacggcacgccctgaggagggcgaggagtg 1951-2025  
20 tgtaacttccggtaggacgtagactccatgaaccacttacaccacctgccgtgcgggactcctcccgctcctcac

cgagg  
gctcc  
2026-2030

25 PCR primers are marked in **bold** (42-1984 = 1942bp).  
Sequencing primers are underlined (GHLCR3.1, 541-558; GHLCR3.2, 1006-1023; GHLCR3.3, 1422-1440;  
GHLCR5.0, 640-658)

Figure 5

	-700	ctgttttcttg	gtttgtgtct	ctgctgcaag	tccaaggagc	tggggcaata	-651
5	-650	ccttgaagtct	gggttcttcg	tcccaggga	cctgggggag	ccccagcaat	-601
	-600	gctcaggga	aggggagagc	aaagtgtggg	gttggttctc	tctagtggtc	-551
	-550	agtgttgaa	ctgcatccag	ctgactcagg	ctgacccagg	agtcctcagc	-501
	-500	agaagtggaa	ttcaggactg	aatcgtgctc	acaacccccca	caatctattg	-451
	-450	gctgtgcttg	gccccctttc	ccaacacaca	cattctgtct	ggtgggtgga	-401
10	-400	ggttaaacat	gcggggagga	ggaaagggat	aggatagaga	atgggatgtg	-351
	-350	gtcggtaggg	ggtctcaagg	actggctatc	ctgacatcct	tctccgcgtt	-301
	-300	cagggtggcc	accatggcct	gcggccagag	ggcaccacag	tgacccttaa	-251
	-250	agagaggaca	agttgggtgg	tatctctggc	tgacactctg	tgacacaacc	-201
	-200	tcacaacact	ggtgacgggtg	ggaaggga	gatgacaagc	cagggggcat	-151
15	-150	tgctccagca	tgtgtgggag	gagcttctaa	attatccatt	agcacagcc	-101
	-100	cgtcagtggc	cccatgcata	aatgtacaca	gaaacagggtg	ggggcagacag	-51
	-50	tgggagagaa	ggggccaggg	tataaaaagg	gcccacaca	gaccagctca	-1
	+1	aggatcccaa	ggcccaactc	cccgaaccac	tcagggtcct	gtggacagct	+50
	+51	cacctagcgg	caATGGCTAC	AGgtaagcgc	ccctaaaatc	cctttgggca	+100
20	+101	caatgtgtcc	tgaggggaga	ggcagcgacc	tgtagatggg	acgggggac	+150
	+151	taaccctcag	gtttggggct	tctgaatgtg	agtatcgcca	tgtaagccca	+200
	+201	gtatttgcc	aatctcagaa	agctcctggt	ccctggaggg	atggagagag	+250
	+251	aaaaacaaac	agctcctgga	gcagggagag	tgctggcctc	ttgctctccg	+300
	+301	gctccctctg	ttgcccctctg	gtttctcccc	agGCTCCCGG	ACGTCCTGCG	+350
25	+351	TGCTGGCTTT	TGGCCTGCTC	TGCTGCTCCT	GGCTTCAAGA	GGGCAGTGCC	+400
	+401	TTCCCAACCA	TTCCCTTATC	CAGGCTTTTT	GACAACGCTA	TGCTCCGCGC	+450
	+451	CCATCGTCTG	CACCAGCTGG	CCTTTGACAC	CTACCAGGAG	TTTgtaagct	+500
	+501	cttggggaa	gggtgcgcac	caggggtggc	aggaaggggt	gactttcccc	+550
	+551	cgctgggaaa	taagaggagg	agactaagga	gctcaggggt	tttccccgaag	+600
30	+601	cgaaaatgca	ggcagatgag	cacacgctga	gtgaggttcc	cagaaaagta	+650
	+651	acaatgggag	ctggtctcca	gcgtagacct	tggtgggagg	tccttctcct	+700
	+701	agGAAGAAGC	CTATATCCCA	AAGGAACAGA	AGTATTCATT	CCTGCAGAAC	+750
	+751	CCCCAGACCT	CCCTCTGTTT	CTCAGAGTCT	ATTCCGACAC	CCTCCACAG	+800
	+801	GGAGGAACA	CAACAGAAAT	CCgtgagtg	atgccttctc	cccaggcggg	+850
35	+851	gatgggggag	acctgtagtc	agagcccccg	ggcagcacag	ccaatgcccc	+900
	+901	tccttcccc	gcagAACCTA	GAGCTGCTCC	GCATCTCCCT	GCTGCTCATC	+950
	+951	CAGTCGTGGC	TGGAGCCCGT	GCAGTTCCTC	AGGAGTGTCT	TCGCCAACAG	+1000
	+1001	CCTGGTGTAC	GGCGCCTCTG	ACAGCAACGT	CTATGACCTC	CTAAAGGACC	+1050
	+1051	TAGAGGAAGG	CATCCAAACG	CTGATGGGGg	tgaggggtggc	gccaggggtc	+1100
40	+1101	cccaatcctg	gagccccact	gactttgaga	gctgtgttag	agaaacactg	+1150
	+1151	ctgccctctt	tttagcagtc	aggccctgac	ccaagagaa	tcaccttatt	+1200
	+1201	cttcatttcc	cctcgtgaat	cctccaggcc	tttctctaca	ccctgaaggg	+1250
	+1251	gagggaggaa	aatgaatgaa	tgagaaaggg	agggaaacag	acccaagcgc	+1300
	+1301	ttggcctctc	cttctcttcc	ttcactttgc	agAGGCTGGA	AGATGGCAGC	+1350
45	+1351	CCCCGGACTG	GGCAGATCTT	CAAGCAGACC	TACAGCAAGT	TCGACACAAA	+1400
	+1401	CTCACACAAC	GATGACGCAC	TACTCAAGAA	CTACGGGCTG	CTCTACTGCT	+1450
	+1451	TCAGGAAGGA	CATGGACAAG	GTCGAGACAT	TCCTGCGCAT	CGTGCACTGC	+1500
	+1501	CGCTCTGTGG	AGGGCAGCTG	TGGCTTCTAG	ctgcccgggt	ggcatccctg	+1550
	+1551	tgaccctcc	ccagtgccct	tcctggccct	ggaagttgcc	actccagtgc	+1600
50	+1601	ccaccagcct	tgctctaata	aaattaagtt	gcatcatttt	gtctgactag	+1650
	+1651	gtgtccttct	ataatattat	gggggtggagg	gggggtggtat	ggagcaaggg	+1700
	+1701	gcaagttggg	aagacaacct	gtagggcctg	cgggggtctat	tcgggaacca	+1750
	+1751	agctggagtg	cagtggcaca	atcttggttc	actgcaatct	ccgcctcctg	+1800
	+1801	ggttcaagcg	attctcctgc	ctcagcctcc	cgagttgttg	ggattccagg	+1850
55	+1851	catgcatgac	caggctcagc	taatttttgt	ttttttggta	gagacggggg	+1900
	+1901	ttcaccatat	tgccagggtc	ggtctccaac	tcctaattctc	aggtgatcta	+1950
	+1951	cccaccttgg	cctcccaaat	tgctgggatt	acaggcggtga	accactgctc	+2000
	+2001	ccttccctgt	ccttctgatt	ttaaaataac	tataccagca	ggaggacgtc	+2050
	+2051	cagacacagc	ataggctacc	tgccatgccc	aaccgggtggg	acatttgagt	+2100
60	+2101	tgcttgcttg	gcactgtcct	ctcatgcgtt	gggtccactc	agtagatgcc	+2150
	+2151	tggtgaattc	ctgggcctag	ggctgtgcc	gctgcctcgt	cccgtcacct	+2200
	+2201	tctggcttct	tctctccctc	catatcttag	ctgttttctc	catgagaatg	+2250
	+2251	ttccaaattc	gaaatttcta	tttaaccatt	atatattttac	ttgtttgcta	+2300

**Figure 5 (continued)**

5	+2301	ttatctctgc	ccccagtaga	ttgttagctc	cagaagagaa	aggatcatgt	+2350
	+2351	cttttgctta	tctagatatg	cccatctgcc	tggtacaatc	tctggcacat	+2400
	+2401	gttacaggca	acaactactt	gtggaattgg	tgaatgcatg	aatagaagaa	+2450
	+2451	tgagtgaatg	aatgaataga	caaaaggcag	aaatccagcc	tcaaagaact	+2500
	+2501	tacagtctgg	taagaggaat	aaaatgtctg	caaatagcca	caggacaggt	+2550
10	+2551	caaaggaagg	aggggctatt	tccagctgag	ggcaccat	caggaaagca	+2600
	+2601	cccagactt	cctacaacta	ctagacacat	ctcgatgctt	ttcacttctc	+2650
	+2651	tatcaatgga	tctctccct	ggagaataat	ccccaaagt	aaattactta	+2700
	+2701	gcacgtccag	ttaggtagat	ccttggtgtac	ttcttggttg	ttcagagatc	+2750
	+2751	atcaaccagt	gcaaacaatc	cccccatcaa	tacacagcag	tgctgcccc	+2800
15	+2801	tctccccccg	aggtcttccg	aggcccttcc	tccgtgcctg	aacccctgg	+2850
	+2851	acatatcata	tggcaaaactg	aagtgtccaa	cgagatatag	gaagtgaaac	+2900
	+2901	acgatgtaca	ctgaaacgtg	caatacaaat	atgcagcatg	aagtgcctcg	+2950
	+2951	gttcactaac	ccgagctacg	ctgggtgctt	cttttctacc	actttcctta	+3000

20

1000 900 800 700 600 500 400 300 200 100 0



**Figure 6**

Growth hormone 1  
 5 Gene symbol : *GH1*  
 Location : 17q

1 2  
 -26 ATG GCT ACA G↓GC TCC CGG ACG TCC CTG CTC CTG GCT TTT GGC CTG -12  
 Met Ala Thr G ly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly Leu

10 -11 CTC TGC CTG CCC TGG CTT CAA GAG GGC AGT GCC TTC CCA ACC ATT 4  
 Leu Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Phe Pro Thr Ile

15 5 CCC TTA TCC AGG CTT TTT GAC AAC GCT AGT CTC CGC GCC CAT CGT 19  
 Pro Leu Ser Arg Leu Phe Asp Asn Ala Ser Leu Arg Ala His Arg

20 CTG CAC CAG CTG GCC TTT GAC ACC TAC CAG GAG TTT ↓ GAA GAA GCC 34  
 Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala

20 35 TAT ATC CCA AAG GAA CAG AAG TAT TCA TTC CTG CAG AAC CCC CAG 49  
 Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln

25 50 ACC TCC CTC TGT TTC TCA GAG TCT ATT CCG ACA CCC TCC AAC AGG 64  
 Thr Ser Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg

65 GAG GAA ACA CAA CAG AAA TCC ↓ AAC CTA GAG CTG CTC CGC ATC TCC 79  
 Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser

30 80 CTG CTG CTC ATC CAG TCG TGG CTG GAG CCC GTG CAG TTC CTC AGG 94  
 Leu Leu Leu Ile Gln Ser Trp Leu Glu Pro Val Gln Phe Leu Arg

95 AGT GTC TTC GCC AAC AGC CTG GTG TAC GGC GCC TCT GAC AGC AAC 109  
 Ser Val Phe Ala Asn Ser Leu Val Tyr Gly Ala Ser Asp Ser Asn

35 110 GTC TAT GAC CTC CTA AAG GAC CTA GAG GAA GGC ATC CAA ACG CTG 124  
 Val Tyr Asp Leu Leu Lys Asp Leu Glu Glu Gly Ile Gln Thr Leu

125 ATG GGG ↓ AGG CTG GAA GAT GGC AGC CCC CGG ACT GGG CAG ATC TTC 139  
 Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr Gly Gln Ile Phe

40 140 AAG CAG ACC TAC AGC AAG TTC GAC ACA AAC TCA CAC AAC GAT GAC 154  
 Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn Asp Asp

45 155 GCA CTA CTC AAG AAC TAC GGG CTG CTC TAC TGC TTC AGG AAG GAC 169  
 Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp

170 ATG GAC AAG GTC GAG ACA TTC CTG CGC ATC GTG CAG TGC CGC TCT 184  
 Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser—

50 185 GTG GAG GGC AGC TGT GGC TTC TAG  
 Val Glu Gly Ser Cys Gly Phe \*

**Figure 7**

GH variant *Glu-Gly30*  
5 Location : 17q

1 2  
-26 ATG GCT ACA G↓GC TCC CGG ACG TCC CTG CTC CTG GCT TTT GGC CTG -12  
Met Ala Thr G ly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly Leu

10 -11 CTC TGC CTG CCC TGG CTT CAA GAG GGC AGT GCC TTC CCA ACC ATT 4  
Leu Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Phe Pro Thr Ile

5 CCC TTA TCC AGG CTT TTT GAC AAC GCT AGT CTC CGC GCC CAT CGT 19  
Pro Leu Ser Arg Leu Phe Asp Asn Ala Ser Leu Arg Ala His Arg

15 20 CTG CAC CAG CTG GCC TTT GAC ACC TAC CAG GAG TTT ↓ GGG GAA GCC 34  
Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Gly Glu Ala

2 3  
35 TAT ATC CCA AAG GAA CAG AAG TAT TCA TTC CTG CAG AAC CCC CAG 49  
Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln

50 ACC TCC CTC TGT TTC TCA GAG TCT ATT CCG ACA CCC TCC AAC AGG 64  
Thr Ser Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg

3 4  
25 65 GAG GAA ACA CAA CAG AAA TCC ↓ AAC CTA GAG CTG CTC CGC ATC TCC 79  
Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser

80 CTG CTG CTC ATC CAG TCG TGG CTG GAG CCC GTG CAG TTC CTC AGG 94  
Leu Leu Leu Ile Gln Ser Trp Leu Glu Pro Val Gln Phe Leu Arg

30 95 AGT GTC TTC GCC AAC AGC CTG GTG TAC GGC GCC TCT GAC AGC AAC 109  
Ser Val Phe Ala Asn Ser Leu Val Tyr Gly Ala Ser Asp Ser Asn

110 GTC TAT GAC CTC CTA AAG GAC CTA GAG GAA GGC ATC CAA ACG CTG 124  
Val Tyr Asp Leu Leu Lys Asp Leu Glu Glu Gly Ile Gln Thr Leu

4 5  
125 ATG GGG ↓ AGG CTG GAA GAT GGC AGC CCC CGG ACT GGG CAG ATC TTC 139  
Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr Gly Gln Ile Phe

40 140 AAG CAG ACC TAC AGC AAG TTC GAC ACA AAC TCA CAC AAC GAT GAC 154  
Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn Asp Asp

155 GCA CTA CTC AAG AAC TAC GGG CTG CTC TAC TGC TTC AGG AAG GAC 169  
Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp

45 170 ATG GAC AAG GTC GAG ACA TTC CTG CGC ATC GTG CAG TGC CGC TCT 184  
Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser

185 GTG GAG GGC AGC TGT GGC TTC TAG  
50 Val Glu Gly Ser Cys Gly Phe \*

Figure 8

WT-HIS vs VAR 14

